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DAVID A JACKSON
KLAUBER & JACKSON
411 HACKENSACK AVENUE
HACKENSACK, NJ 07601

EXAMINER	
WILSON, MICHAEL C	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/485,943	FRIEDMAN ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *124,132-137,139-143,145-151,155-159 and 163-175* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *124,132-137,139-143,145-151,155-159 and 163-175* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7-3-06 has been entered.

Claims 1-123, 125-131, 138, 144, 152-154 and 160-162 have been canceled. Claims 174 and 175 have been added.

Contrary to applicants statement on pg 21, the first sentence under "Status of the Claims", claims 124, 132-137, 139-143, 145-151, 155-159 and 163-175 are pending and under consideration in the instant office action.

Applicant's arguments filed 7-3-06 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

The scope of the preamble of the methods claimed should match the scope of the results in the methods. Claim 124, for example, should begin "A method of decreasing the body weight" to properly reflect the functional limitation in the body of the

claims. All of the claims should be limited to a method of "decreasing the body weight" of a mammal.

Specification

The amendment filed 7-3-06 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The concept of "83 percent" on pg 12, lines 15-2, and on pg 102, lines 15-17, is new matter. Applicants argue the phrase has support in the comparison of the disclosed amino acid sequences of mouse and human OB polypeptides in Figure 4. Applicants' argument is not persuasive. Percent identity can be measured using numerous methods. It is not readily apparent that applicants' new calculation used the same method as the one originally used or that 84% as originally disclosed was simply a calculation error. Changing the percentage from 84 to 83 is new matter unless applicants establish the original calculation was in error and that using the same original method used to calculate identity reveals the proper result is 84 percent. Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

Enablement

Claims 124, 132-137, 139-143, 145-149, 155-159 and 163-173 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Breadth of the claims

The claims are drawn towards a method of modifying the weight of a mammal using a vector encoding an ob protein under conditions that provide for expression of the ob protein in vivo. The ob proteins in the claims include SEQ ID NO: 2 (mouse ob), SEQ ID NO: 4 (human ob) and variations thereof (see claims for details regarding the variations). The preamble of the claim 124 requires "modifying the body weight of a mammal". The body of the claim requires administering the vector to a mammal "wherein the vector is administered in a therapeutically effective amount such that the mammal exhibits a decrease in body weight". Therefore, administration of a vector encoding ob must decrease body weight to have an enabled use according to the specification.

State of the art regarding the ob gene/protein

The obese (ob) gene product is equivalent to the leptin gene product (Tartaglia, 1995, Cell, Vol. 83, pages 1263-1271; see abstract, line 1; see the instant application on pg 5, lines 5-16).

Ob/ob mice with a homozygous disruption in the ob gene were known to be obese (pg 3, lines 3-6).

At the time of filing, it was unknown whether obese ob/ob mice correlated to obese humans with a gene mutation. Since the time of filing, Clayton (Arch. Dis. Child,

1998, Vol. 78, 278-284) taught that 5% of humans with obesity have an ob concentration lower than expected (pg 282, col. 1, line 20).

The specification states: "Because of the myriad factors that seem to impact body weight, it has not been possible to predict which factors and, more particularly, which homeostatic mechanisms is actually primarily determinative. Nonetheless, the apparent connections between the ob gene and the extent and characteristics of obesity have prompted the further investigation and elucidation that is reflected by the present application. It is the identification of the sequence of the gene and corresponding peptide materials, to which the present invention following below directs itself." (pg 4, lines 14-20).

Thus, it was unpredictable whether ob/ob mice correlated to any obese human or to a gene disruption that occurred in humans.

At the time of filing, the art did not teach what tissue expressed the ob protein. Nor did the art teach in what tissues the ob protein mediated an effect. Since the time of filing, Tartaglia (cited above, Dec. 29, 1995, Cell, Vol. 83, pages 1263-1271) confirmed that up to 1995, the tissue in which the ob protein mediated an effect remained unknown (pg 1263, col. 2, line 2).

Thus, the tissue target required to express ob or to mediate a decrease in body weight in a mammal was unknown at the time of filing.

Since the time of filing, Fletcher (Nov. 15, 1995, Blood, Vol. 86, page 241a) taught decreasing the body weight of an obese mouse having a homozygous mutation in the ob gene by administering bone marrow from an autologous mouse transduced

with a retroviral vector encoding ob to the bone marrow of the recipient mouse (page 241a, line 12).

Morsy (1998, Proc. Natl. Acad. Sci., USA, Vol. 95, pages 7866-7871) taught that 60% weight loss can be obtained for 6-7 weeks following administration of a leptin-encoded adenoviral vector (pg 7870, col. 1, line 13); however, analysis revealed eventual loss of the vector DNA 4 and 8 weeks following administration of the vector (pg 7870, col. 2, line 5).

Unpredictability of gene therapy

At the time of filing and since, the combination of vector, promoter, dosage, target tissue, level of expression and route of administration required to target the desired tissue so that a therapeutic would occur was unpredictable.

Feldman (Fundamental & Clinical Pharmacology, 1995, Vol. 9, pg 8-16) suggested treating restenosis using a vector encoding a protein. Feldman discussed experiments in which the vector administered to the arterial wall during angioplasty allowed low levels of protein expression in cells of the arterial wall. Feldman taught that obtaining a therapeutic effect was prevented by low numbers of cells expressing a transgene, transfection efficiency, target specificity, and sustained expression (pg 12, "Arterial gene therapy"). None of the experiments described by Feldman resulted in a therapeutic effect.

Miller (Feb. 1995, FASEB J., Vol. 9, pg 190-199) reviewed the types of vectors available for *in vivo* gene therapy, and concluded that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be

advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (pg 198, col. 1). Miller did not obtain a therapeutic effect using gene delivery.

Crystal (Oct. 20, 1995, Science, Vol. 270, pg 404-410) also reviewed various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (pg 409). Crystal did not obtain a therapeutic effect using gene delivery.

Verma (Sept. 1997, Nature, Vol. 389, pg 239-242) reviewed vectors for use in gene therapy and discussed problems associated with adenoviral vectors and indicates a resolution to vector targeting has not been achieved in the art (see entire article). Verma also taught appropriate regulatory elements may improve expression, but it is unpredictable what regulatory elements target what tissues (pg 240, sentence bridging col. 2-3). Verma did not obtain a therapeutic effect using gene delivery.

Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69) indicated that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviewed new techniques under experimentation in the art that show promise but stated that such techniques were even less efficient than viral gene delivery that failed to work (see pg 65, 1st ¶ under "Conclusion"). Deonarain did not obtain a therapeutic effect using gene delivery.

Ross (Sept. 1996, Human Gene Therapy, Vol. 7, pg 1781-1790) stated a major technical impediment to gene transfer is the lack of ideal gene delivery systems including vectors, promoters and modes of delivery (pg 1782, col. 2, 1st full ¶). The ability to use gene therapy to obtain a therapeutic effect in a patient was unpredictable (Ross, pg 1789, col. 1, 1st ¶). Ross did not obtain a therapeutic effect using gene delivery.

Therefore, it was unpredictable what combination of vector, promoter, dosage, cells, level of expression and route of administration would provide a therapeutic effect using gene delivery.

Teachings of the specification

Pg 5, line 10 teaches the "leptin" protein is absent in plasma of ob/ob mice. The specification does not teach the leptin protein is absent in obese humans.

The specification on pg 73-83 describes protein-based therapy for obesity. On pg 74, lines 18-27, applicants describe administering the ob protein by intravenous, intraarterial, intraperitoneal, intramuscular or subcutaneous routs of administration. Pg 83, line 3, through pg 84, line 24, describes administering the ob gene using a vector to decrease body weight of a mammal. The description of nucleic acid-based therapies on pg 83 does not include a description of the conditions required to obtain expression of the protein or the route of administration. The disclosure on pg 74 is limited to protein administration and does not include vector administration. One of skill in the art would not read the description of routes of administration for proteins on pg 74 as applying to the nucleic acid-based therapy on pg 83 because they are under different headings (see

headings for "Polypeptide-based therapeutic treatment" and "Nucleic acid-based therapeutic treatments" on pg 73 and 83, respectively). The specification does not teach any specific dosages or routes of delivery for the vectors listed for use in *in vivo* gene delivery.

Pg 83, line 4, teaches the ob gene can be "introduced into human fat cells to develop gene therapy for obesity." The specification does not teach how to target vectors to adipocytes using *in vivo* gene delivery. The specification does not teach what cells mediate the function of the ob protein so that one of skill could target a vector encoding ob to those cells.

Pg 83, lines 3-26, lists viral vectors for delivering the ob gene. For example, defective viral vectors allow "for administration to cells in a specific, localized area, without concern that the vector can infect other cells. Thus, adipose tissue can be specifically targeted." Such vectors include HSV, papillomavirus, EBV adenovirus, AAV and retrovirus. Pg 84, lines 1-17, describes introducing a vector by lipofection. Pg 84, lines 18-24 describe administering the vector as naked DNA plasmid. The specification does not teach the specific combination of vector, promoter, route of administration and dosage required to obtain ob expression in a mammal such that a decrease in body weight is obtained.

Pg 90 begins the examples section, which include gene mapping of the mouse and human ob gene, cloning of the mouse and human ob gene, preparing the ob protein, preparing antibodies to the ob protein and recombinant expression of the ob protein in bacteria.

Pg 118, line 23, pg 12, line 10, through pg 125, line 2, and pg 125, Table 1, teach administering the ob protein to three strains of ob/ob mice. The ob/ob mice lost weight.

Pg 129, Example 9, and pg 126, Example 10, describe increased expression of ob in adipocytes as compared to other tissues. Since the time of filing, it has been confirmed that ob was expressed exclusively in adipose tissue (Clayton, cited above, pg 282, col. 1, line 3).

Pg 144, line 22, and pg 120, lines 1-25, describe the ob serum levels in mice and humans.

Pg 147, Example 11, teaches the human ob protein is active in ob/ob mice.

The specification teaches delivering ob protein to treat obesity on pg 73-74 but does not provide adequate guidance for one of skill to obtain the same serum level ob using gene delivery.

Rejection

Overall, the specification does not overcome the unpredictability in the art by teaching the specific combination of vector, promoter, dosage and route of administration required to target ob expression to fat cells or how to express ob protein so it will target the tissue that mediates a reduction in body weight.

Since the time of filing, Fletcher (cited above) decreased the body weight of an obese mouse having a homozygous mutation in the ob gene by administering bone marrow from an autologous mouse transduced with a retroviral vector encoding ob to the bone marrow of the recipient mouse (page 241a, line 12). In view of the unpredictability in the art of gene therapy, the specific combination of retrovirus,

transduced bone marrow cells and bone marrow administration is essential to the invention. Applicants do not enable the claimed invention because applicants do not describe the specific combination of retrovirus, transduced bone marrow cells and bone marrow administration, which is essential to reduce body weight as taught by Fletcher.

Morsy (cited above) obtained weight loss by administering 1-2 x 10^{11} particles of helper adenoviral vector encoding leptin via the tail vein of ob/ob mice (pg 7869, col. 2; pg 7870, Fig. 4B, Fig. 5B, col. 1). In view of the unpredictability in the art of gene therapy, the specific combination of adenovirus, tail vein injection and the dosage of 1-2 x 10^{11} particles is essential to the invention. Given the state of the art regarding the ob gene/protein taken with the teachings in the specification, one of skill would not have expected intravenous administration to cause ob expression in adipocytes as contemplated by applicants as being the source of ob expression. Nor would one of skill have known that intravenous administration would cause ob expression capable of targeting cells that mediate a therapeutic effect. Applicants do not enable the claimed invention because the specification does not describe the specific combination of adenovirus, tail vein injection and the dosage of 1-2 x 10^{11} particles, which is essential to reduce body weight as taught by Morsy.

Muzzin of record (PNAS, Dec. 1996, Vol. 93, pg 14804-14808) obtained weight loss of ob/ob mice by administering 3 x 10^{9} particle forming units of helper adenoviral vector encoding leptin via the tail vein (pg 14805, ¶ bridging col. 1-2 and col. 2, 1st full ¶). In view of the unpredictability in the art of gene therapy, the specific combination of adenovirus, tail vein injection and the dosage of 3 x 10^{9} pfu is essential to the invention.

One of skill would not have expected that intravenous administration would cause expression in adipocytes as contemplated by applicants as the source of the majority of ob expression. Nor would one of skill have expected that intravenous administration would cause ob expression capable of targeting cells capable of mediating a decrease in body weight. Applicants do not enable the claimed invention because the specification does not describe the specific combination of adenovirus, tail vein injection and the dosage of 3×10^9 pfu, which is essential to reduce body weight as taught by Muzzin.

In view of the art recognized unpredictability in gene therapy and the mere list of possible vectors provided by applicants on pg 83 and 84 without teaching the route of administration or dosage, those of skill in the art would be left to perform an undue amount of experimentation to determine the specific combination of vector, promoter, route of administration and dosage required to reduce body weight in a mammal.

Furthermore, the claims encompass decreasing the body weight of any mammal using a vector encoding an ob protein. However, the specification and the art since the time of filing are limited to treating mammals with an ob deficiency with the ob protein. The specification does not correlate the obese mammals having a defective ob gene to any other obese mammals or any other obesity related gene defect. The specification does not provide an enabled use for decreasing the body weight of a wild-type mammal (having a normal weight). Therefore, it would require one of skill undue experimentation to determine how to use the vector encoding ob to treat obesity in any mammal as broadly claimed other than those with a defective ob gene.

Certain claims encompass using any analog of an ob protein that modulates body weight. The specification defines analogs as ob proteins that agonize or antagonize the function of the ob protein. In other words, the claims encompass administering a vector encoding a protein that antagonizes the function of the ob protein and causes a weight increase. The specification does not teach any ob proteins that antagonize the function of ob. The specification does not teach how to use the ob protein analogs to increase weight. Without such guidance it would require one of skill in the art undue experimentation to determine antagonistic analogs of the ob protein or how to use vectors encoding ob proteins capable of increasing body weight.

The specification does not enable using a vector encoding an ob protein having any substitution as broadly encompassed by 134, 135, 142, 143, 148, 149, 158, 159 and 165-173. Salvador (Exp. Opin. Pharmacotherapy, 2001, Vol. 2, No. 10, pg 1615-1622) taught leptin is 167 amino acids in length and has the body weight control functions confined to amino acids residues 106-140. The specification teaches the conservative and non-conservative substitutions between the mouse and human leptin proteins in Fig. 4. The specification does not define what they consider "conservative" and "non-conservative" substitutions. The specification does not teach the functional region of the leptin protein or that any substitution as broadly claimed will allow the leptin protein produced to control body weight. Without such guidance it would have required one of skill undue experimentation to determine which amino acids could be substituted without altering the active site of leptin or to determine which amino acids

could be substituted without altering the structure of the active site or the function of leptin.

Response to applicants' arguments

Applicants acknowledge the isolation, cloning, sequencing and analysis of the OB gene and protein are the subject of applicant's invention (pg 21 of response filed 7-3-06). Applicants' acknowledgement fails to imply gene therapy as claimed is the subject of applicants' invention.

Applicants argue those of skill could readily determine which tissues expressed OB. Applicants' argument is not persuasive and unfounded. The specification does not disclose any assays that would reveal the tissues in which OB was expressed or mediated its effects. Applicants do not point to a reference that first discloses the tissues in which OB was expressed or mediated its effects and confirms that the methods of doing so were well known at the time of filing the instant application. Tartaglia (cited above) confirmed that in December 1995, the tissue in which the ob protein mediated an effect remained unknown (pg 1263, col. 2, line 2). Therefore, applicants' assertion that the tissues in which OB was expressed and mediated an effect could be determined without undue experimentation is unfounded. More importantly, applicants have not adequately taught how to target OB expression to its native expressing tissue or to target OB to the tissue in which it mediates its effects. Determining the tissue to target is only the first of a number of hurdles applicants have left for those of skill to perform the method claimed.

Applicants argue Fletcher, Morsy and Muzzin used leptin gene therapy to treat ob/ob mice after the time of filing. Therefore, applicants conclude that the broad statement in the specification as originally filed were enabling. Applicants' argument is not persuasive. The specific combination of vector and route of administration described by Fletcher, Muzzin et al. are not disclosed in the specification as originally filed. Applicants did not teach the specific combination of vector, route of administration, etc. required to overcome the unpredictability in the art and decrease body weight using leptin gene therapy. Such parameters are essential for enabling the method because the combination of elements required to obtain a therapeutic effect using gene therapy was unpredictable.

Applicants argue the references that do not directly relate to leptin gene therapy. Applicants' argument is not persuasive. Feldman, Miller, Crystal, Verma and Deonarain establish the state of the art of gene therapy in general providing examples in various areas that did not have a therapeutic effect in vivo. Morsy, Muzzin and Fletcher cannot taught leptin gene therapy, but cannot be relied upon for enablement because they were not available at the time of filing and taught factors that were not disclosed in the instant application as originally filed.

In particular, applicants argue Feldman required expressing a gene in arterial walls; applicants conclude Feldman is irrelevant to the claimed invention. Applicants' argument is not persuasive. Feldman knew the target tissue but did not get a therapeutic effect using gene therapy. Thus, Feldman establishes that even if one of skill knew the target tissue of interest, they would have to determine how to deliver DNA

to the target the tissue of interest such that a therapeutic effect was obtained. The instant application fails to provide adequate guidance for those of skill to deliver DNA encoding OB to the target the tissue of interest in a mammal such that the body weight of the mammal was reduced as claimed.

Applicants argue one of skill would have been able to administer any of the vectors listed on pg 83-85 to a host. Applicants' argument is not persuasive. The list of vectors is not adequate to determine which tissue to target, how to target the tissue of interest, whether the vector is capable of providing therapeutic levels of expression of OB or the promoter required to obtain therapeutic levels of OB expression in the tissue of interest. While many vectors were known in the art and could be administered to a mammal, the specification does not provide adequate guidance for those of skill to overcome the unpredictability in the art of gene therapy by providing an adequate roadmap to those of skill to use any vector encoding leptin to reduce the body weight of a mammal as claimed. Such a roadmap would include the tissue of interest, route of administration and dosage required for each vector to obtain therapeutic levels of leptin expression but is missing from the instant application.

Applicants argue Chen (1996), Murphy (1997), Buettner (2000), Dube (2002) and Larcher (2001) enable the claimed invention because they all successful reduced body weight using vectors encoding leptin. Applicants' argument is not persuasive. The references were not available at the time of filing and cannot be relied upon for enablement. The references teach factors that were not disclosed in the specification as originally filed; therefore, the teachings in the references cannot be used to indicate

the specification as originally filed enabled leptin gene therapy. Chen, for example, taught using 60 bp of leptin cDNA 5' untranslated and 76 bp of 3' untranslated as well as the translated region. The leptin coding region was placed in an adenoviral vector under the control of the CMV promoter. The resulting adenovirus was administered via a tube into the carotid artery in the dosage of $1x10^{12}$ PFU. The teachings of Chen, Murphy, etc. are not in the specification as originally filed. The methods of Chen, Murphy, etc. are not readily to those of skill in the art at the time of filing from applicants' disclosure as originally filed.

Applicants argue the combination of elements, particularly the dosage and route of administration, are not essential to perform the methods claimed. Applicants argue it is well within the skill of the artisan to test and determine them. Applicants' argument is not persuasive. Feldman, Miller, Crystal, Verma and Deonarain tested various combinations of elements but failed to obtain a therapeutic effect. Applicants' assertion that the combination of dosage and route of administration required to decrease body weight of a mammal using gene therapy is unfounded and cannot be supported by post-filing evidence that teaches parameters not originally disclosed. For example, the specification does not teach or reasonably imply that administration of adenovirus encoding OB to the carotid artery as described by Chen was capable of decreasing body weight. Nor does the specification reasonably teach or imply that administration of AAV encoding OB to the muscle as described by Murphy was capable of decreasing body weight.

The examples of OB gene therapy provided by applicants were not available at the time of filing and do not reasonably correlate to the teachings in the specification as originally filed. The work done by others since the time of filing may have been inventive. The specification as originally filed does not reasonably teach the combination of elements required to decrease body weight in a mammal using a vector encoding OB.

New Matter

Claims 124, 132-137, 139-143, 145-149, 155-159 and 163-173 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection regarding the phrase "conditions that provide for expression of the OB polypeptide in vivo" in claims 124, 132-135, 163-165 and 167 under new matter has been withdrawn in view of the amendment.

The rejection of claim 151 regarding the concept of administering viral vectors by infection or liposome mediated transfection under new matter has been withdrawn in view of the amendment.

The rejection of claim 160 regarding the concept of using the early or late SV40, CMV, vaccinia, polyoma, adenovirus, 3-phsphoglycerate kinase or other glycolytic

enzyme promoters for gene delivery in a mammal under new matter has been withdrawn because the claim has been canceled.

The rejection regarding the substitutions in claim 165 has been withdrawn because pg 32, line 26, through pg 33, line 10, supports substituting the serine at position 53 or 98 with glycine, alanin, valine, cysteine, methionine or threonine or substituting the arginine at position 92 with asparagine, et al. as claimed.

The phrase "operatively linked to a promoter" in claims 124, 132-135, 139-143, 145-149, 155-159, 163-173 is new matter. Pg 51, lines 8-16, describes coding sequences "under the control" of transcriptional and translational control sequences. The scope of such sequences is not the same as "operatively linked to a promoter." Furthermore, the expression control sequences described on pg 52, line 7, through pg 53, line 15, are limited to in vitro expression of ob because they are part of the description of unicellular hosts for producing the protein *in vitro* (see pg 52, line 2; "yeast" on line 19; pg 53, lines 9-15; pg 54, lines 7-9). The scope of "promoter" is narrower in scope than "transcriptional and translation control sequences" as originally contemplated in the specification as originally filed and is new matter.

The concept of "83 percent or more amino acid identity to the OB polypeptide amino acid sequence set out in SEQ ID NOs: 2, 4, 5, 6, 23 or 25" in claim 133 and 147 remains new matter. Applicants argue the phrase has support in the comparison of the disclosed amino acid sequences of mouse and human OB polypeptides in Figure 4. Applicants' argument is not persuasive. Percent identity can be measured using numerous methods. It is not readily apparent that applicants' new calculation used the

same method as the one originally used or that 84% as originally disclosed was simply a calculation error. Changing the percentage from 84 to 83 is new matter unless applicants establish the original calculation was in error and that using the same original method used to calculate identity reveals the proper result is 84 percent. The amendments to the specification on pg 12, lines 15-2, and on pg 102, lines 15-17, are new matter because they also change 84 to 83 percent.

The concept of an OB protein comprising "amino acids 22-167 of SEQ ID NO: 4 wherein one or more amino acids selected from the group consisting of amino acids 53... ...166 is substituted with another amino acid" in claims 134, 142, 148 and 158 is new matter. Fig. 4 describes specific conservative substitutions of the amino acids of the mouse and human ob polypeptide using asterisks at amino acids 53, 92, 98, 118, 121, 122, 126-128, 132, 139, 159 and 166 and specific non-conservative substitutions using a dash at amino acids 71, 85, 89, 110, 129, 157 and 163. The specification is limited to specific amino acid difference at the positions claimed (except 56 and 95) and does not suggest substituting amino acids at the positions claimed with any amino acid as broadly claimed; therefore, substituting amino acids at the positions claimed with any amino acid as broadly claimed is new matter.

Applicants argue the concept is readily apparent from Fig. 4 and that the specific amino acids that differ between human and mouse are noted in Figure 4 and are those listed in claims 134, 142, 148 and 158. Applicants' argument is not persuasive. Fig. 4 is limited to specific substitutions, i.e. it notes conservative and non-conservative amino acid differences when comparing human and mouse OB proteins. Fig. 4 does not

contemplate substituting the amino acids marked with a * or – with any amino acid as broadly claimed.

The concept of an OB protein comprising "amino acids 22-167 of SEQ ID NO: 4 wherein one or more amino acids selected from the group consisting of amino acids... ...56... [and] ...95... is substituted with another amino acid" in claims 134, 142, 148 and 158 is new matter. Amino acids 56 and 95 do not have a * or – and are not different in mouse and human OB (see Figure 4) or contemplated as being substituted. Applicants do not argue this rejection. It is unclear why the amino acids at positions 56 and 95 are included in the list claimed.

The concept of an OB protein comprising "amino acids 22-166 of SEQ ID NO: 6 wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162 and 165 is substituted with another amino acid" in claim 135, 143, 149, 159 is new matter. The specification does not suggest substituting the amino acids in the Gln deleted mutants in Fig. 5 and 6, specifically with any amino acid as broadly claimed. It is not readily apparent that the conservative and non-conservative differences between the mouse and human protein in Fig. 4 are places for substituting amino acids in the Gln mutants in Fig. 5 and 6, specifically with any amino acid as broadly claimed. Applicants argue the proteins in Fig. 5 and 6 are Gln deletion mutants of the proteins in Fig. 5 and that the numbering of the amino acids for the gln mutants is one less than the numbering in the wild-type in Fig. 4. Therefore, applicants conclude it is readily apparent that the same amino acids in the Gln mutants can be substituted as described

in Fig. 4 and are 1 less in number than those in Fig. 4. Applicants' argument is not persuasive. Fig. 4 is limited to comparing the differences between the human and mouse OB protein and does not contemplate substituting the amino acids marked with a * or – with any amino acid as broadly claimed.

Claims 166-173 remain new matter. Applicants argue the claims have support on pg 32, line 15 through pg 35, line 11. Applicants' argument is not persuasive. The specific substitutions in claim 166, 170, 171 and 173 cannot be found on pg 32, line 26, through pg 32, line 10. For example, the specification does not contemplate substituting one or more aspartic acid residues with glutamic acid. The N-terminal amino acids in claims 167 and 168 cannot be found. The "truncated analogs" with the substitutions listed in claims 169, 172 cannot be found. Please point to specific support for each substitution claimed.

Written Description

Claims 124, 132-137, 139-143, 145-149, 155-159 and 163-173 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 124, 132-137, 139-143, 145-149, 155-159 and 163-173 as newly amended are rejected because the specification does not provide written description for the "therapeutically effective amount" of a vector administered to a mammal "such that the

mammal exhibits a decrease in body weight" or how to administer a vector to a mammal in vivo capable of "modifying the body weight of a mammal" as claimed. While it is readily apparent that the specification contemplates gene delivery, it is not readily apparent that applicants had overcome the unpredictability in the art and knew the specific conditions required to obtain therapeutic levels of ob expression *in vivo* using gene delivery. Pg 51, lines 16-25, discusses DNA operatively linked to expression control sequences. Pg 52, lines 9-17, discusses transforming a unicellular host and using a start codon. Pg 72, line 25, through pg 73, line 2, defines "therapeutically effective amount" i.e. an amount sufficient to cause an improvement in a clinically significant condition in the host; however, the specific combination of vector, dose and route of administration required to reduce body weight using leptin gene therapy is not disclosed. For example, pg 83, line 4, is limited to introducing the ob gene into human fat cells. Therefore, it is not readily apparent that applicants were in possession or could reasonably have determined the combination of elements required to administer a vector in a "therapeutically effective amount such that the mammal exhibits a decrease in body weight" or to "modify[ing] the body weight of a mammal" as claimed.

An adequate written description of a method of gene therapy requires more than a mere statement that delivery of a therapeutically effective amount of vector is part of the invention and reference to a list of possible routes of administration, vectors and promoters used in the method; what is required is a description of the specific combination of vector, promoter, and route of administration capable of having a decreasing body weight. It is not sufficient to define an amount solely by its principal

biological property, i.e. a therapeutically effective amount because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of the combination of vector, promoter, route of administration and dosage required to decrease body weight. Also, naming a type of material generically known to exist, in the absence of knowledge as to what materials are capable of decreasing body weight, is not a description of that material. Thus, claiming all therapeutic effective amounts of a vector that decrease body weight without defining the specific combination of vector, promoter, route of administration and dosage required to do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific DNA sequences, which provide the means for practicing the invention.

Indefiniteness

The rejection regarding the phrase "such OB encoding DNA" in claim 140 lacking antecedent basis has been withdrawn in view of the amendment.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER